Smallpox

As you know, smallpox vaccine is once again being administered to American citizens. Some of you may be administering the vaccine, or may have been asked to consider receiving the vaccine. In this segment of the program we will discuss issues related to smallpox vaccine – specifically, the characteristics of the vaccine, adverse reactions, and contraindications. We will not discuss smallpox disease, or vaccine administration during this program. There are other publications and materials available for this, which will be listed on our broadcast resource website.

As many as three different smallpox vaccines are available, or will soon be available, in the United States. All three vaccines contain the New York City Board of Health strain of live **vaccinia** virus. Smallpox vaccine does **not** contain smallpox, or variola virus. Vaccinia virus is in the same family as smallpox, but is much less pathogenic. When we say smallpox vaccine, we are actually talking about a vaccine that contains vaccinia virus. The only smallpox vaccine available now in the United States is Dryvax. This vaccine was produced in the early 1980s by Wyeth Lederle. Dryvax was produced from calf lymph containing live vaccinia virus. This vaccine is provided as a freeze dried powder and contains the antibiotics polymyxin B, streptomycin, tetracycline and neomycin. The diluent used to reconstitute the vaccine is 50% glycerin with a small amount of phenol as a preservative.

The newest vaccines also contain live New York City Board of Health strain of vaccinia virus, but are produced using cell culture technology rather than live animals. These vaccines will be distributed as a freeze dried powder but do not contain antibiotics. The diluent contains glycerin and phenol, like the Dryvax diluent. These new vaccines have not yet been licensed by the Food and Drug Administration.

Smallpox vaccine is unique in that it is not administered by injection. It is administered into the superficial layer of the skin with a two pronged, or bifurcated, needle like this one. Bifurcated needles are supplied in individual sterile packages with the vaccine. A local reaction at the site of inoculation, like the one shown here, indicates a successful vaccination. In addition to a pustule, the local reaction at the site of inoculation can be very dramatic. In several recent studies of old and new vaccines given to unvaccinated adults, the average size of the pustule at 2 weeks after vaccination was 12 millimeters – or about half an inch. The average size of erythema surrounding the pustule was 16 to 24 millimeters, and average induration was 11 to 15 millimeters, or up to two thirds of an inch. Some vaccinees may have larger amounts of erythema and induration that can be mistaken for cellulitis. This is called a robust reaction, and is a normal variant, seen in 5% to 15% of vaccinees. It can occur both in people being vaccinated for the first time, and people being revaccinated many years after

prior vaccination. These reactions generally improve within 24 to 72 hours without specific therapy. 40% to 47% of the vaccinees reported mild pain at the site of inoculation. 2% to 3% reported the pain as severe. Axillary lymphadenopathy was reported in about one third of recipients. Most lymphadenopathy was mild, but in 3% to 7% it was considered moderate – that is, bothersome to the vaccinee but not otherwise interfering with normal activities.

Fever is common after administration of smallpox vaccine. About 10% of unvaccinated adults report a fever of 100^{o} Fahrenheit or higher, and 3% report temperature of 102^{o} or higher. Fever is most common 8 to 10 days after vaccination. In addition to fever, up to one third of adult vaccinees also report a variety of constitutional symptoms, including headache, myalgias, chills, nausea, and fatigue on or about the eighth or ninth day after vaccination. 1% or 2% of recipients reported these symptoms as severe.

Beginning about 4 days after vaccination, vaccinia virus is present at the site of inoculation. If the lesion is touched, virus can be transferred to another part of the body. Transfer, or autoinoculation, of vaccinia from the vaccination site is called inadvertent inoculation. This is the most frequent complication of smallpox vaccination. Inadvertent inoculation accounted for about half of all complications of primary vaccination and revaccination. In studies of smallpox vaccination in 1968, inadvertent autoinoculation occurred at a rate of 25 to 529 cases per million primary vaccinations. This has also been the most common complication of the current civilian smallpox vaccination program. Careful site care will significantly decrease the risk of this complication. Lesions of inadvertent inoculation can occur anywhere on the body, but the most common sites usually involved are the face, eyelid – as you see here – nose, mouth, genitalia, and rectum.

A variety of erythematous or urticarial rashes occur approximately 10 days after primary vaccination. They are flat, erythematous, macular, or urticarial lesions, usually with microscopic vasculitis. The pathophysiology of these rashes is not well understood. The rashes usually do not become vesicular, and do not appear to involve viral multiplication or systemic dissemination. The rash resolves spontaneously within 2 to 4 days. This child has erythema multiforme related to smallpox vaccine. Although the skin involvement may be extensive, patients with erythematous or urticarial rashes associated with vaccinia are generally not severely ill and are usually afebrile. On rare occasions Stevens-Johnson syndrome, or bullous erythema multiforme may develop.

Another type of rash following smallpox vaccination is called generalized vaccinia. This condition is believed to result from a vaccinia viremia with implantations of the virus in the skin in people without underlying illness. True generalized vaccinia consists of vesicles or pustules appearing on normal skin distant from the vaccination site, and may be accompanied by symptoms, such as fever, headache, and myalgias. In the 1968 studies, rashes diagnosed as generalized vaccinia occurred at a rate of 23 to 242 cases per million primary vaccinations. This is generalized vaccinia involving the left leg. Most rashes labeled as generalized vaccinia produce only minor illness with little residual

damage. The rash is generally self-limited and usually requires no specific therapy.

In general local reactions, nonspecific rashes, and mild cases of inadvertent inoculation and generalized vaccinia do not require specific therapy. We will discuss treatment of more severe reactions a little later.

Three complications of smallpox vaccination are rare, but can be very severe or fatal. These are eczema vaccinatum, progressive vaccinia, and postvaccinial encephalitis. Eczema vaccinatum is the generalized spread of vaccinia on the skin of a person with eczema or true atopic dermatitis, or a history of eczema or atopic dermatitis. The most serious cases among vaccine recipients occur among primary vaccinees. Severity is independent of the activity of the underlying eczema. Severe cases have also been observed among contacts of a recently vaccinated person with someone who has eczema or atopic dermatitis. Eczema vaccinatum occurred at a rate of 10 to 39 cases per million primary vaccinations. This woman has eczema vaccinatum. She had eczema and acquired the infection after contact with her recently vaccinated boyfriend. She survived the illness but had extensive residual scarring of her skin. Eczema vaccinatum is believed to result from either blood dissemination of vaccinia virus or by direct skin inoculation of vaccinia on skin affected by eczema or atopic dermatitis. Vaccinia virus is readily recoverable from skin lesions.

This woman has progressive vaccinia, also known as vaccinia necrosum. Progressive vaccinia is a severe, potentially fatal illness, characterized by a nonhealing vaccination site with progressive necrosis. Metastatic lesions are often present. Progressive vaccinia occurs almost exclusively among persons with cellular immunodeficiency, but can occur in persons with humoral immunodeficiency. Progressive vaccinia can occur following revaccination of persons who have become immunosuppressed since their primary vaccination. In the 1968 studies, progressive vaccinia occurred at a rate of 0.9 to 1.5 cases per million primary vaccinations. Progressive vaccinia could be seen more often in today’s population, with the greater prevalence of HIV and post transplant immunosuppression.

A major unpredictable complication is postvaccinial central nervous system disease. In the majority of cases, postvaccinial CNS disease usually affects primary vaccinees 12 months of age or younger, and adolescents and adults receiving a primary vaccination. It presents with any of a variety of CNS signs, such as ataxia, confusion, paralysis, seizures, or coma. Most cases are believed to result from autoimmune or allergic reactions, similar to other postviral CNS syndromes rather than direct viral invasion of the nervous system. Approximately 15% to 25% of vaccinees with this complication died, and 25% developed permanent neurological sequelae. It occurred at a rate of 3 to 12 cases per million primary vaccinations. One suspected case of postvaccinial CNS disease has been reported during the current smallpox vaccination program.

A fetus may be infected if a pregnant woman receives smallpox vaccine. Smallpox vaccine is the **only** vaccine ever shown to injure a fetus. Fetal vaccinia

is a rare complication of smallpox vaccination. Fewer than 50 cases of fetal vaccinia infection have been reported. When this complication did occur, it was usually following primary vaccination of the mother in the second or third trimester. Fetal infection following vaccination in the first trimester would presumably result in spontaneous abortion. But studies are contradictory as to whether an increased number of spontaneous abortions actually occurred in pregnant women. Smallpox vaccine is not known to cause congenital malformation. Although a few pregnant women have been inadvertently vaccinated during the current smallpox vaccination program, no cases of fetal vaccinia have occurred.

Death resulting from smallpox vaccination is rare, with approximately 1 death per million primary vaccinations and 1 death per 4 million revaccinations. Death is most often the result of postvaccinial CNS disease or progressive vaccinia. However, death can also result from eczema vaccinatum.

Vaccinia immune globulin, or VIG, has been used to successfully treat some smallpox vaccine complications. It is a sterile solution of the immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine. VIG is not currently licensed by FDA, so must be administered using an investigational new drug protocol. VIG is recommended for the treatment of severe inadvertent inoculation. Severe means a large number of lesions, toxicity, or substantial pain. VIG is also recommended for the treatment of eczema vaccinatum, severe generalized vaccinia, and progressive vaccinia. VIG is not recommended for mild inadvertent inoculation, mild generalized vaccinia or for nonspecific rashes, such as erythema multiforme. It provides no benefit in the treatment of postvaccinial CNS disease or in the treatment of smallpox.

It is important that smallpox vaccine adverse reactions be monitored carefully, and reported promptly. State Health Departments and CDC are tracking the number of vaccinations administered and the occurrence of adverse reactions through both active and passive surveillance. Clinicians who suspect that a smallpox vaccine recipient, or the contact of a recipient, may be experiencing an adverse reaction should report it to the state health department. The event should also be reported to the Vaccine Adverse Event Reporting System, or VAERS.

CDC published guidance for clinicians on smallpox vaccination and adverse reactions in February 2003 in *Morbidity and Mortality Weekly Report*. There is link to this document on our broadcast resources website. It is also available from the National Immunization Program online publication system.

There is also an extensive amount of information on smallpox vaccine adverse reactions on the CDC smallpox website. If you are involved in the smallpox vaccination program, you should be familiar with these materials.

Because of the risk of adverse reactions, it is extremely important that persons administering smallpox vaccine be aware of contraindications to vaccination. The

contraindications and precautions that I will discuss are applicable for situations of non-emergency use of smallpox vaccine. In an outbreak, for persons exposed or potentially exposed to a person with smallpox, there are **no** contraindications to vaccination.

Smallpox vaccine contains live vaccinia virus, which is administered into the superficial layers of the skin. A successful vaccination produces a lesion on the skin that contains vaccine virus for up to 3 weeks. The vaccine virus can be transmitted to household and other close contacts. In the absence of smallpox cases, candidates for vaccination must be carefully screened for contraindications. Certain medical conditions in the person's household contacts must also be considered as contraindications for vaccination.

As with all vaccines, smallpox vaccine is contraindicated for persons who have experienced a severe allergic reaction to a vaccine component or following a prior dose of vaccine. By severe allergic reaction, we mean anaphylaxis or symptoms of an anaphylaxis-like reaction, such as generalized urticaria, wheezing, or difficulty breathing. In addition to live vaccinia virus, reconstituted Dryvax vaccine contains trace amounts of the antibiotics polymyxin B, streptomycin, tetracycline, and neomycin. The diluent also contains phenol as a preservative. Persons with severe allergy to any of these products should not be vaccinated. The newer cell culture vaccines do not contain antibiotics. No smallpox vaccine available in the United States contains penicillin.

Persons with significant immunosuppression, should not receive smallpox vaccine. Replication of vaccinia virus can be enhanced among people with immunodeficiency diseases and immunosuppression, and result in serious adverse reactions. Persons with household contacts who are immunosuppressed should also not be vaccinated in nonemergency situations, because the recent vaccination site contains live virus that can be transmitted to other individuals. Significant immunosuppression can be caused by many diseases, including leukemia, lymphoma, generalized malignancy; solid organ or stem cell transplantation; and humoral or cellular immunity disorders, including HIV infection. It has been reported that some persons with severe clinical manifestations of some autoimmune diseases, such as systemic lupus erythematosis, may have some degree of immunosuppression as a component of the disease. So people with immunodeficiency as a clinical component of an autoimmune disease should not receive smallpox vaccine during the pre-event vaccination program. Drugs and therapy that can cause immunosuppression include alkylating agents, antimetabolites, radiation, or high dose corticosteroid therapy. Prednisone doses of 2 milligrams per kilogram of body weight per day or higher or 20 milligrams per day or higher for 14 days or more should be considered immunosuppressive. Persons who have taken high dose corticosteroids should not be vaccinated within one month of completing therapy. Those treated with other immunosuppressive drugs should not be immunized for 3 months after their last dose. There are other drugs that may be immunosuppressive, such as interferon and drugs used after transplants to suppress tissue rejection. Persons taking these drugs should not be vaccinated. If there is any doubt if the drug or condition is immunosuppressive, the person

should not be vaccinated. The person should be referred to their treating physician to determine whether or not immunosuppression is present.

Live viral vaccines are contraindicated during pregnancy. Smallpox vaccine should not be administered to pregnant women or persons with pregnant household contacts for nonemergency indications. Pregnancy should also be avoided for at least 4 weeks after vaccination. Women who are breastfeeding should not be vaccinated, because the close contact that occurs during this activity could increase the chance of transmission of the vaccine virus to the breastfeeding infant.

Because of the increased risk for eczema vaccinatum, smallpox vaccine should not be administered to persons with eczema or atopic dermatitis or a past history of these conditions. Persons who have a **household contact** with eczema or atopic dermatitis or a history of these conditions should also not be vaccinated. Persons with other types of acute, chronic, or exfoliative skin conditions, such as psoriasis, contact dermatitis, or herpes zoster might be at higher risk for disseminated skin rashes from the vaccine, although these rashes are generally not as severe as eczema vaccinatum. Persons with exfoliative skin conditions should not be vaccinated until the condition resolves.

Children less than 12 months of age should not be vaccinated. All vaccinated persons should take precautions to prevent virus transmission to young children and other household contacts. The ACIP smallpox statement recommends that children younger than 18 years should not be vaccinated. During the current smallpox vaccination program only healthcare and public health response team volunteers are being vaccinated. It is not likely that anyone younger than 18 years would qualify for a response team. So 18 years is the functional minimum age for vaccination now. As with all vaccines, smallpox vaccination should be deferred for people with moderate or severe acute illness.

Soon after the 2003 smallpox vaccination programs began a variety of cardiac events began to be detected among vaccinated persons. Symptoms ranged from those of myocarditis and pericarditis to ischemic symptoms, such as angina pectoris, and myocardial infarction. Myocarditis and pericarditis had been reported following smallpox vaccination in the 1950s and 1960s, but were usually associated with vaccinia strains not used in the U.S. vaccine. The incidence of these conditions among vaccine recipients was not known with certainty. The onset of myopericarditis in relation to smallpox vaccination, and the frequency of the reports among vaccinated persons, suggests that the association may be real. The association of other cardiac events, such as myocardial infarction is biologically plausible, but data are insufficient to determine if there is a causal relationship.

As a precautionary measure, CDC recommends that persons diagnosed as having a heart condition, with or without symptoms, should not be vaccinated at this time. These conditions include known coronary artery disease, angina or myocardial infarction, congestive heart failure, cardiomyopathy, chest pain or

shortness of breath with activity, stroke or transient ischemic attack, and other heart conditions being treated by a doctor, such as valvular heart disease. In addition, persons should not receive smallpox vaccine if they have 3 or more risk factors for heart disease, including hypertension, hypercholesterolemia, diabetes, a first degree relative with a heart condition before the age of 50, or being a current smoker. Persons with suspected cardiac events following smallpox vaccination will continue to be investigated. In addition, we strongly encourage clinicians caring for vaccinated persons to promptly report suspected adverse events to their state health departments.

There is an additional precaution unique to smallpox vaccine. People with inflammatory eye diseases may be at increased risk for inadvertent inoculation due to touching or rubbing the eye. So it may be prudent to defer vaccination of persons with inflammatory eye diseases requiring steroid treatment until the condition resolves and the course of therapy is complete.

A careful medical history for contraindications to vaccination should be done for every person prior to vaccination. Additional information about contraindications and precautions for smallpox vaccine, including the smallpox Vaccine Information Statement and screening forms are available on the CDC websites.

We do not have time on this program to discuss smallpox vaccine administration. Detailed information, including a video, is available through our broadcast resources website.